PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

COCKBAIN, J.
FRANK B. DEHN & CO.
179 Queen Victoria Street
London EC4V 4EL
GRANDE BRETAGNE

EJ

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	25.01.99
Applicant's or agent's file reference: 42.67973.jc	**REPLY DUE** within **3 month(s)** from the above date of mailing

International application no.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/01261	30/04/1998	30/04/1997

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
FORSKNINGSPARKEN I S AS et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This report contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and / or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.6.

DUE DATE8 NOTED
25/4/99

If **no reply is filed**, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 30/08/1999

Name and mailing address of the international preliminary examining authority
European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer / Examiner
Tikorn, A-C

Formalities officer (incl. extension of time limits)
Hebert, W
Telephone No. (+49-89) 2399-8161

WRITTEN OPINION

International application No. PCT/GB98/01261

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-39 as originally filed

Claims, No.:

1-17 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement (NOT)

1. Statement

Novelty (N)	Claims	
Inventive step (IS)	Claims	7-17
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section V:

1 The following documents are referred to in this communication:

D1: Proc. Natl. Acad. Sci USA (3/1997) **94** 2150-2155
D2: Science (1995) **270** (5235) 467-470
D3: WO 95 20681

D1 deals with the use of cDNA microarrays for the discovery and analysis of inflammatory disease-related genes. The microarray was designed for the identification of known human genes of probable significance. A cDNA library was used to amplify target regions by PCR (page 2150 col 2 para 3 - page 2151 col 1 para 1). The purified PCR products were immobilized and hybridized with mRNA of interest. Due to fluorescent labels the amount of hybridizing mRNA was quantified by scanning (page 2151 col 2 para 1).
With this method differential expression in cultured cell lines was monitored (page 2152 col 2 para 2 - page 2153 col 2 para 2; Fig. 2).

D2 discloses a method for monitoring gene expression patterns with a cDNA microarray starting with 2 μg of total mRNA. The method comprises isolating mRNA from tissue or cells, preparing cDNA probes, immobilizing the cDNA on glass microscope slides (page 467 col 3 para 2), hybridizing the cDNA with labelled mRNA or cDNA of interest and quantifying the hybridized cDNA of interest with a fluorescence scanner (page 467 col 3 para 3 - page 468 col 2 para 1). The method is also proposed for diagnostic purposes (page 469 col 3 para 3).

D3 describes a method of comparative gene transcript analysis useful for diagnostics (page 12 para 2). Gene transcripts from patients' fluids or tissues are isolated and expanded. A sequence specific analysis (page 12 para 2; Examples 6.4-6.5) allows the comparison with sequence databases (page 12 para 2). Moreover the quantification compared against reference database sequence abundances including normal data sets for diseased and healthy patients is disclosed.

2 Claims 1-17 appear to be new in the sense of Article 33(2) PCT. The preparation

of a non-sequence-dependent transcript pattern on the basis of the entire mRNA population in combination with the quantification of transcripts in normal and diseased mRNAs/cDNAs according to the present invention is not disclosed in the available documents.
The same applies to the dependent claims 2-6.

Claims 7-9 relate to kits, that are prepared on the basis of the gene transcript pattern (claims 1-5) and are thus considered to be novel (Article 33(2) PCT). The same applies to the use of the kits (claim 10).

Claims 11-13 relate to a method of preparing a standard diagnostic gene transcription pattern applying a kit as defined in claims 7-9 and are thus also considered to be novel. For the same reason it appears that claims 14-17 fulfil the requirements of Article 33(2) PCT.

3 Claims 7-17 do not appear to fulfil the requirements of Article 33(3) PCT. Although prepared by a different method, the microarray disclosed in D1 appears to contain at least 2 probes specific for a disease (page 2150 col 2 para 3). A skilled person would develop a kit containing the solid support (microarray plates) with the immobilized probes in order to apply the method of D3. The provision of known reagents in a packaged form cannot in general be regarded as involving an inventive step (claims 7-10).
Moreover the skilled person is able to prepare a standard diagnostic gene transcript pattern with the kit described in claims 7-9, thus claims 11-13 do also not appear to be inventive (Article 33(3) PCT).
The identification or diagnosis of a disease with the help of the kit described in claims 7-9 (claims 14-17) appears to be common technology for a skilled person and does not appear to involve an inventive step (Article 33(3) PCT).

4 Claims 1-6 appear to fulfil the requirements of Article 33(3) PCT.
The closest prior art, D1, relates to microarrays for the diagnosis of diseases. The mRNA of the reference sample is used to construct a cDNA library. From this library single clones of probable significance are selected (page 2150 col 2 para 3), immobilized and used for hybridization of mRNAs or cDNAs of interest (page 2151 col 2 para 1).

The problem to be solved over D1 can be regarded as how to provide a method of preparing a gene transcript pattern probe kit taking account of differential gene expression on the basis of the entire population of mRNA (application: page 13 para 2) and mRNA species present in the diseased sample and not in the normal sample (application: page 15 para 2).
The problem is solved in the present invention by separation of the gene transcripts of normal and diseased cells by a non-sequence-dependent method before comparing the expression patterns of normal and diseased mRNAs and selecting clones.
The method disclosed in D3 involves the selection of clones of a cDNA library that are subjected to sequence-specific analysis and then compared against reference database. Thus the comparison of normal and diseased mRNA is based on a reduced population of gene transcripts. Even if the skilled person would combine D1 with D3 he would not obtain the subject-matter of the present invention. Therefore claims 1-6 appear to be inventive (Article 33(3) PCT).

Section VII:

- The reference to non-published patent applications should be changed to publication numbers throughout the application (e.g. page 2 para 4) (cf. Guidelines C-II 4.17a)

- The reference given on page 38 para 1 is not complete, as the editor and publisher are not indicated.

Section VIII:

5 Claim 1 does not seem to fulfil the requirements of Article 6 PCT, as it appears that an essential feature is missing. In the description it is disclosed, that in order to carry out the invention it is necessary to identify a signal corresponding to each transcript/cDNA (page 13 para 4) in order to be able to select mRNA or cDNA species (step d) (Guidelines C-III, 4.3).

6 The category of claims 16 and 17 is not clear (Article 6 PCT). The claims should relate either to a method or to a kit (Guidelines C-III, 4.1).

EPA/EPO/OEB
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Correspondence with the EPO on PCT Chapter II demands

In order to ensure that your PCT Chapter II demand is dealt with as promptly as possible you are requested to use the enclosed self-adhesive labels with any correspondence relating to the demand sent to the Munich Office.

One of these labels should be affixed to a prominent place in the upper part of the letter or form etc. which you are filing.

European Patent Office
D-80298 München
Germany

20 April 1999

42.7.67973.jc

BY FACSIMILE

Dear Sirs

International Patent Application No. PCT/GB98/01261
in the name of Forskningsparken i Ås AS et al

I refer to the Written Opinion dated 25 January 1999, relating to the above mentioned application.

An amended set of claims is filed herewith, together with amended replacements of pages 38 and 39 of the description. Duplicate copies follow with the confirmation copy of this letter.

Regarding the individual points raised by the Examiner, I would comment as follows:

Section V.3

The Examiner has raised lack of inventive step objections against claims 7 to 17 in light of documents D1 and D3. In response to this objection, claim 7 has been amended to recite that the probe species which form part of the kit are identified according to the method as defined in any one of claims 1 to 5. The basis for this amendment may be found on page 3, lines 7 to 10 of the description as filed. Since the Examiner has acknowledged that the method of identifying probe species in claims 1 to 5 is inventive, probe species identified according to the invention are similarly inventive and are not comparable to the probes isolated according to D1. Furthermore, kits which incorporate probe species identified in an inventive manner should be considered to be inventive. It is therefore respectfully submitted that this revised claim (and the claims which depend upon it) relates to subject matter which is inventive.

Lack of inventive step objections have also been raised against claims 11 to 13 and 14 to 17, which relate to the use of a kit as claimed in claims 7 to 9. As mentioned above, the kit claims comprise the requisite inventive step and thus by their dependency on the kit claims, claims 11 to 13 and 14 to 17 should similarly be considered inventive.

Section VII

The Examiner has pointed out that the reference to non-published patent applications should be changed to publication numbers. However, at page 2, paragraph 4, the patent application is already referred to by publication number WO95/20681. Clarification of this objection would be appreciated.

The reference given on page 38, paragraph 1, has been completed to list the editors and publisher as requested.

Section VIII

In relation to the Examiner's suggestion, claim 1, part (d), has been amended to make reference to identifying a signal corresponding to each mRNA or cDNA, based on the specification at page 13, last paragraph.

I would be grateful if you would acknowledge safe receipt of this letter and enclosures by returning to me one copy of the enclosed Form 1037.

Yours faithfully,
Frank B. Dehn & Co.

Elizabeth Jones

Encs:

jyf

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

COCKBAIN, J.
FRANK B. DEHN & CO.
179 Queen Victoria Street
London EC4V 4EL
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	29.06.99
Applicant's or agent's file reference 42.67973.jc	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/01261	30/04/1998	30/04/1997

Applicant
FORSKNINGSPARKEN I S AS et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Digiusto, M Tel.(+49-89) 2399-8162

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
42.67973.jc		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/01261	30/04/1998	30/04/1997
International Patent Classification (IPC) or national classification and IPC		
C12Q1/68		
Applicant		
FORSKNINGSPARKEN I S AS et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/11/1998	29.06.99
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Tilkorn, A-C Telephone No. (+49-89) 2399 8688

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/01261

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-37	as originally filed			
38,39	as received on	22/04/1999	with letter of	20/04/1999

Claims, No.:

1-17	as received on	22/04/1999	with letter of	20/04/1999

Drawings, sheets:

1/3-3/3	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-17
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-6
	No:	Claims 7-17
Industrial applicability (IA)	Yes:	Claims 1-17
	No:	Claims

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section V:

1. The following documents are referred to in this communication:

D1: Proc. Natl. Acad. Sci USA (3/1997) **94** 2150-2155
D2: Science (1995) **270** (5235) 467-470
D3: WO 95 20681

D1 deals with the use of cDNA microarrays for the discovery and analysis of inflammatory disease-related genes. The microarray was designed for the identification of known human genes of probable significance. A cDNA library was used to amplify target regions by PCR (page 2150 col 2 para 3 - page 2151 col 1 para 1). The purified PCR products were immobilized and hybridized with mRNA of interest. Due to fluorescent labels the amount of hybridizing mRNA was quantified by scanning (page 2151 col 2 para 1).
With this method differential expression in cultured cell lines was monitored (page 2152 col 2 para 2 - page 2153 col 2 para 2; Fig. 2).

D2 discloses a method for monitoring gene expression patterns with a cDNA microarray starting with 2 μg of total mRNA. The method comprises isolating mRNA from tissue or cells, preparing cDNA probes, immobilizing the cDNA on glass microscope slides (page 467 col 3 para 2), hybridizing the cDNA with labelled mRNA or cDNA of interest and quantifying the hybridized cDNA of interest with a fluorescence scanner (page 467 col 3 para 3 - page 468 col 2 para 1). The method is also proposed for diagnostic purposes (page 469 col 3 para 3).

D3 describes a method of comparative gene transcript analysis useful for diagnostics (page 12 para 2). Gene transcripts from patients' fluids or tissues are isolated and expanded. A sequence specific analysis (page 12 para 2; Examples 6.4-6.5) allows the comparison with sequence databases (page 12 para 2). Moreover the quantification compared against reference database sequence abundances including normal data sets for diseased and healthy patients is disclosed.

2. **Claims 1-17** appear to be new in the sense of Article 33(2) PCT. The preparation

of a non-sequence-dependent transcript pattern on the basis of the entire mRNA population in combination with the quantification of transcripts in normal and diseased mRNAs/cDNAs according to the present invention is not disclosed in the available documents.
The same applies to the dependent claims 2-6.

Claims 7-9 relate to kits, that are prepared on the basis of the gene transcript pattern (claims 1-5) and are thus considered to be novel (Article 33(2) PCT). The same applies to the use of the kits (claim 10).

Claims 11-13 relate to a method of preparing a standard diagnostic gene transcription pattern applying a kit as defined in claims 7-9 and are thus also considered to be novel. For the same reason it appears that claims 14-17 fulfil the requirements of Article 33(2) PCT.

3. **Claims 7-17** do not appear to fulfil the requirements of Article 33(3) PCT.
Although prepared by a different method, the microarray disclosed in D1 appears to contain at least 2 probes specific for a disease (page 2150 col 2 para 3). Hence, the 2 probes identified and used in the method of D1 may be identical with the probes identified and used according to claim 7 of the present application as both, the probes according to D1 and the probes according to claim 7 of the present invention are derived from disease-related genes and thus belong to a disease-related transcription pattern. A new and inventive method does not necessarily entail a new and inventive product.
A skilled person would develop a kit containing the solid support (microarray plates) with the immobilized probes in order to apply the method of D3. The provision of known reagents in a packaged form cannot in general be regarded as involving an inventive step (claims 7-10).
Moreover the skilled person is able to prepare a standard diagnostic gene transcript pattern with the kit described in claims 7-9, thus claims 11-13 do also not appear to be inventive (Article 33(3) PCT).
The identification or diagnosis of a disease with the help of the kit described in claims 7-9 (claims 14-17) appears to be common technology for a skilled person and does not appear to involve an inventive step (Article 33(3) PCT).

4. **Claims 1-6** appear to fulfil the requirements of Article 33(3) PCT.
The closest prior art, D1, relates to microarrays for the diagnosis of diseases. The mRNA of the reference sample is used to construct a cDNA library. From this library single clones of probable significance are selected (page 2150 col 2 para 3), immobilized and used for hybridization of mRNAs or cDNAs of interest (page 2151 col 2 para 1).
The problem to be solved over D1 can be regarded as how to provide a method of preparing a gene transcript pattern probe kit taking account of differential gene expression on the basis of the entire population of mRNA (application: page 13 para 2) and mRNA species present in the diseased sample and not in the normal sample (application: page 15 para 2).
The problem is solved in the present invention by separation of the gene transcripts of normal and diseased cells by a non-sequence-dependent method before comparing the expression patterns of normal and diseased mRNAs and selecting clones.
The method disclosed in D3 involves the selection of clones of a cDNA library that are subjected to sequence-specific analysis and then compared against reference database. Thus the comparison of normal and diseased mRNA is based on a reduced population of gene transcripts. Even if the skilled person would combine D1 with D3 he would not obtain the subject-matter of the present invention. Therefore claims 1-6 appear to be inventive (Article 33(3) PCT).

Section VIII:

The category of claims 16 and 17 is not clear (Article 6 PCT). The claims should relate either to a method or to a kit (Guidelines C-III, 4.1).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 98/ 01261	30/04/1998	30/04/1997
Applicant		
FORSKNINGSPARKEN I ÅS AS et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [X] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established by this Authority to read as follows:

   METHOD OF PREPARING A STANDARD DIAGNOSTIC GENE TRANSCRIPT PATTERN

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/01261

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHENA M ET AL: "QUANTITATIVE MONITORING OF GENE EXPRESSION PATTERNS WITH A COMPLEMENTARY DNA MICROARRAY" SCIENCE, vol. 270, no. 5235, 20 October 1995, pages 467-470, XP000644675 cited in the application see the whole document ---	1-17
X	WO 95 20681 A (INCYTE PHARMA INC) 3 August 1995 cited in the application see esp. claims and examples --- -/--	1-17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 September 1998	22/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Müller, F

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/01261

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	HELLER R. A. ET AL.,: "Discovery and analysis of inflammatory disease-related genes using cDNA microarrays" PROC. NATL. ACAD. SCI. USA, vol. 94, - March 1997 pages 2150-2155, XP002076789 cited in the application see whole document, esp. discussion ---	1-17
X	EP 0 534 640 A (PFIZER) 31 March 1993 see the whole document -----	1-17

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/01261

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9520681 A	03-08-1995	AU 688465 B	12-03-1998
		AU 1694695 A	15-08-1995
		BG 100751 A	31-07-1997
		BR 9506657 A	16-09-1997
		CA 2182217 A	03-08-1995
		CN 1145098 A	12-03-1997
		CZ 9602189 A	14-05-1997
		EP 0748390 A	18-12-1996
		FI 962987 A	26-09-1996
		JP 9503921 T	22-04-1997
		LV 11696 B	20-08-1997
		NO 963151 A	27-09-1996
		PL 315687 A	25-11-1996
		HU 75550 A	28-05-1997
EP 0534640 A	31-03-1993	AT 143700 T	15-10-1996
		CA 2078703 A	24-03-1993
		DE 69214243 D	07-11-1996
		DE 69214243 T	06-02-1997
		DK 534640 T	17-03-1997
		ES 2092056 T	16-11-1996
		FI 924242 A	24-03-1993
		GR 3021721 T	28-02-1997
		JP 2703156 B	26-01-1998
		JP 5192199 A	03-08-1993
		US 5643730 A	01-07-1997

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/01160

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Nucleic Acids Research, Volume 19, No. 25, issued 1991, E. Hara et al, "Subtractive cDNA cloning using oligo($dT)_{30}$-latex and PCR: isolation of cDNA clones specific to undifferentiated human embryonal carcinoma cells", pages 7097-7104, see entire document.	1-16
X --- Y	Nature Genetics, Volume 2, No. 3, issued November 1992, K. Okubo et al, "Large scale cDNA sequencing for analysis of quantitative and qualitative aspects of gene expression", pages 173-179, see narrative text portion of entire document.	1, 3 --- 2 and 4-16